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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/585,541	06/02/2000	Reiner Gentz	1488.1030004	6732

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EXAMINER
SISSON, BRADLEY L

ART UNIT	PAPER NUMBER
1634	7

DATE MAILED: 02/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/585,541	GENTZ ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-78* is/are pending in the application.

4a) Of the above claim(s) *69 and 70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-68 and 71-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Group 1630, Art Unit 1634.

Election/Restrictions

2. Applicant's election with traverse of formulations comprising amino acids Ser(69) to Ser(208) of SEQ ID NO: 2, claims 1-68 and 71-78, in Paper No. 6 is acknowledged. The traversal is on the ground(s) that there is no serious burden placed upon the examiner by searching all other formulations comprising any f the other polypeptides. Argument is also presented "that the members of the Markush groups of the pending claims are sufficiently few in number and very closely related, as they are all different *portions of the same amino acid sequence*, so that a search of all of the members may be made without serious burden ..." (emphasis in the original). This is not found persuasive because the claims are not drafted to where the amino acid sequence of any two polypeptides is required to be from differing portions of the same sequence. While applicant has directed attention to SEQ ID NO: 2 as being a base sequence, it is noted that none of the claims are limited to SEQ ID NO: 2, or specific portions thereof. While the specification may recite certain limitations, such are not necessarily read into the claims, but rather, the claims are read as broadly as is reasonably possible. To that end, it is noted that the specification at page 28, lines 20-27 and also at page 30 clearly state that the KGF-2 polypeptide can have any number and variety of mutations and modifications, including the

introduction of classical and non-classical amino acids, just so long as the essential characteristic of the polypeptide is retained. Accordingly, applicant use of various names to identify a polypeptide where the sequence of same is not clearly set forth, has been interpreted to encompass a broad genus of polypeptides that only have some undefined property in common. In light of the breadth of just what constitutes a "KGF-2 polypeptide," each and every polypeptide that makes up the genus of "KGF-2 polypeptides" is considered to be a distinct chemical compound.

3. Acknowledgement is made of applicant's referral to the MPEP 804.04 to the extent that "nucleotide sequences that encode the same protein are not considered to be independent and distinct inventions and will continue to be examined together." As shown above, the claimed sequences are not required to be the same and as such constitute different chemical entities and are independent and distinct inventions.

4. The requirement is still deemed proper and is therefore made FINAL.

Specification

5. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179

USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

6. The attempt to incorporate subject matter into this application by reference to provisional and non-issued US Patent applications is improper because these incorporated documents were referenced as providing a description of the proteins encompassed by the claims.

7. The disclosure is objected to because of the following informalities: The current status of all referenced applications needs to be updated.

8. Appropriate correction is required.

Claim Objections

9. Claims 1-68 and 71-78 are objected to because of the following informalities: They have been found to encompass non-elected embodiments and as such, need to be narrowed to the elected invention. Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-68 and 71-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. For purposes of examination, the elected invention, *i.e.*, polypeptides comprising amino acids Ser(69) to Ser(208) of SEQ ID NO: 2, have been interpreted as allowing for the addition of other amino acids, including non-classical amino acids which flank the sequence set forth by Ser(69) to Ser(208) of SEQ ID NO: 2. Support for this interpretation is based upon the disclosure where at pages 28 and 30 applicant explicitly teaches that the amino acid sequence can be modified in various ways. Upon review of the disclosure, it appears that applicant has isolated by a single polypeptide (SEQ ID NO: 2) and has identified "particularly preferred" deletion mutants of same; see pages 36-37 of the disclosure. The specification does not support the position that an adequate written description exists for the addition of any other molecules, be they amino acids or some other molecule, to either end of the polypeptide. In support of this position, attention is directed to the decision of *Vas-Cath Inc. v. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

> This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 USC 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

12. Claims 1-68 and 71-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As presently worded, the claims are all drawn to a pharmaceutical composition that is to comprise a polypeptide comprising amino acids Ser(69) to Ser(208) of SEQ ID NO: 2. As

presently worded, the polypeptide composition need not have any property. Review of the disclosure finds support for the concept that the polypeptide is to be useful in topical and injectable formulations where it is used in soft-tissue growth and regeneration is desired. The specification has not been found to set forth a reproducible procedure whereby any one of the myriad polypeptides, much less the claimed polypeptide composition has been demonstrated to show application of same, either topically or via injection, has resulted in soft tissue growth or regeneration, regardless of the type or location of soft tissue in an individual, or the type of individual (human and non-human).

13. The specification has not been found to enable the manufacture and use of alternative polypeptide compositions, i.e., those pharmaceutical compositions tht comprise the elected polypeptide wherein said polypeptide has flanking residues and/or modified sequences. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which can be tolerated in a protein's amino acid sequence and still retain similar biological activity requires a (1) knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which re conserved (*i.e.*, expectantly intolerant to modification), and (2) detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determination to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the real of routine experimentation.

14. One of the main considerations to be made in determining whether undue experimentation is required is the amount of experimentation required. See *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). Even if substitutions with the natural 20 amino acids encoded by DNA were the only modifications, instant claims would still broadly encompass a multitude of species; calculated as 20^N * (length)!/N/(length-N)! wherein "20" is the number of natural amino acids encoded by DNA, "N" is the number of positions where substitutions can occur, "!" is the factorial symbol, "/" is the division symbol and "length" is the total number of amino acids in the protein or peptide. In putting these numbers in perspective, it is noted that the earth is estimated to have existed for 10^{17} seconds (see Creighton, T.E. 1983. Proteins: Structure and Molecular Principles, W. H. Freeman and Company, NY. 93-94, page 94, paragraph 1). There are an estimated 10^{79} atoms in the universe (page 231 of Creighton, Prog. Bophys. Molec. Biol. 33:231-233, 1975). A polypeptide chain of 100 amino acids could exist in 10^{130} combinations and "just one molecule of each of these different proteins would fill the entire [known] universe 10^{27} times over, even if packed together in the most efficient manner" (see paragraph 1, page 94 of 1983 Creighton reference).

15. While recombinant and mutagenic techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar biological activity are limited in any protein. The result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g., multiple substitutions. The sequence of some proteins

is highly conserved and one skilled in the art would not expect tolerance to any amino acid modifications in such proteins.

16. The specification does not support the broad scope of the claims which encompass all modifications and fragments because the specification does not disclose the following:

a. The amino acid sequence for the claimed protein (while SEQ I DNO: 2 is defined, the additional sequences encompassed by the term "comprising" are not defined);

b. The general tolerance to modification and extent of such tolerance;

c. The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;

d. What fragments, if any, can be made which retain the biological activity of the intact protein; and

e. The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

17. Thus, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims, broadly including any number of additions, deletions, or substitutions and fragments of any size. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').

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> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 38, 44, 76, and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

20. Claim 38 is indefinite with respect to just what effect one is to stabilize against in determining a "stabilizing amount."

21. The term "high" in claim 44 is a relative term that renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining

the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

22. Claims 76 and 78 are indefinite with respect to just what constitutes "a reaction product thereof."

Double Patenting

23. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

18. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

19. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 1-68 and 71-78 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-81 of U.S. Patent No. 6,238,888 B1.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are dawn to pharmaceutical compositions that comprise the elected polypeptide species.

Claim Rejections - 35 USC § 101

21. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 1-68 and 71-78 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. As presently worded, the polypeptide of the pharmaceutical composition does not have to have any capacity to cause or promote soft-tissue growth and regeneration, the only disclosed utility. Applicant is urged to consider amending the claims such that the polypeptide has a specific activity.

Conclusion

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

23. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

24. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

bls
February 12, 2002